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Volume XVI NOVEMBER 1955 Number 11

DISEASES OF THE NERVOUS SYSTEM

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

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VOL. XVI NOVEMBER 1955 No. 11

Published monthly by
PHYSICIANS POSTGRADUATE PRESS
277 Broadway, New York 7, New York

EDITORIAL OFFICES
UNIVERSITY OF TEXAS SCHOOL OF MEDICINE
800 Avenue B., Galveston, Texas

Entered as second-class matter at the Post Office at New York, N. Y.

DISEASES of the NERVOUS SYSTEM

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

Peripheral Electrical Stimulation, a New Form of Psychiatric Treatment

(A Preliminary Report)

CHARLES H. JONES, M.D.
Sedro Woolley, Washington
JAMES G. SHANKLIN, M.D., HENRY H. DIXON, M.D.,
J. M. BROOKHART, PH.D., and PAUL H. BLACHLY, M.D.
Portland, Oregon

Peripheral electrical stimulation has been directly evolved as a clinical application of the findings of Blachly and Brookhart[1] in their animal experiments with unidirectional currents (nonconvulsive electroshock) in barbiturate coma.

Nonconvulsive electroshock therapy was originally developed by Delmas-Marsalet[2] in 1943 and later, independently, by Hirschfeld[3] in 1949. In reporting upon the therapeutic effectiveness of this form of treatment, both workers suggest that the associated autonomic phenomena are due to selective stimulation of the diencephalon. Hence, the preference for the term, nonconvulsive transcerebral electrostimulation. Hirschfeld presents as evidence for transcerebral stimulation the observation that electrode placements allowing connecting lines to pass the diencephalic regions usually result in strong autonomic and emotional responses, whereas, other electrode placements such as the bifrontal do not. While good therapeutic results have been obtained from nonconvulsive electroshock by those workers[3,4,5] who have recognized that it acts in a different manner than convulsive electroshock, much has remained obscure as to the way unidirectional electrical currents bring about such improvements.

Alexander[5] first tried unidirectional currents of low amperage as a method of overcoming states of apnea, laryngeal spasm and other immediate complications of convulsive electroshock therapy. He noted that not only did the added nonconvulsive component of the treatment relieve respiratory and circulatory complications of convulsive electroshock but also profound changes occurred in his patients' behavior. They became more active, showed less memory defect and, in particular, experienced less postshock anxiety. Alexander further extended his clinical observations to include the use of the Funkenstein test in selecting patients for various physiological therapies. Alexander notes that nonconvulsive electroshock modifies the Funkenstein test in a manner opposite to that of convulsive electroshock. He concludes that nonconvulsive electroshock is indicated only in those mentally ill patients showing central sympathetic hyperreactivity and is specifically contraindicated in those showing central sympathetic hyporeactivity. Experience at Northern State Hospital[6] tends to support Alexander's conclusions that the

Read at the 15th Annual Meeting of the North Pacific Society of Neurology and Psychiatry, Victoria, B.C., March 25, 1955.

clinical effects of nonconvulsive electroshock are opposite to those of convulsive electroshock.

The painful nature of cranially applied unidirectional currents led Hirschfeld to adopt sodium pentothal anesthesia as a pretreatment procedure. With this anesthetic it has been commonly observed that nonconvulsive currents are markedly effective in stimulating respiration. Thus, Robie[7] and others have used nonconvulsive currents to maintain respiration in patients with barbiturate poisoning.

In organizing their animal experiments with barbiturate coma, Blachly and Brookhart were highly skeptical of the hypothesis that cranially applied unidirectional currents stimulated respiration through a direct transcerebral route to the diencephalon. They made numerous kymographic records showing the rate and amplitude of respiration of dogs in deep barbiturate coma before, during and after stimulation with currents supplied by a Reiter CW-47B Electrostimulator. They conclusively demonstrate that such currents modify respiration in a variety of electrode placements on the cranium. The most effective point of stimulation on the head appears to be the snout. However, when the sensory nerves to the head are cut, no effect on respiration can be produced by the currents. Furthermore, stimulation of the dogs' hind legs results in identical effects on respiration and arousal as is obtained through cranial electrodes on intact animals. Thus, from the work of Blachly and Brookhart it appears that unidirectional currents applied to the head modify respiration via peripheral sensory pathways rather than through transcerebral routes as previously suggested.

The demonstration that peripheral electrical stimulation can control the rate and depth of respiration and produce arousal of dogs from barbiturate coma is in harmony with the concept advanced by Moruzzi and Magoun[8] that afferent stimuli mediate arousal by means of the reticular activating system. In view of the fact that nonconvulsive electroshock acts in a way opposite to that of convulsive electroshock, the question arises whether arousal brought about by excitation of the reticular activating system might not underly the central autonomic homeostasis and the behavioral changes which develop in mentally ill patients successfully treated by the nonconvulsive method. Accordingly, we have proceeded to investigate the therapeutic effects of unidirectional electrical currents applied peripherally to a selected group of mentally ill patients.

In developing the technique of treatment to be described, five cooperative patients were selected at random for initial trials. Three were midway through courses of convulsive electroshock and two had completed courses of such treatment. Also, we tried certain procedures on ourselves. To begin with, an attempt was made to parallel Alexander's method of giving nonconvulsive electrostimulation with the single exception of electrode placement. Instead of placing electrodes on the anesthetized patient's head, they were fastened over the distal third of the calves. Maximum amperages compatible with satisfactory respiration were used with the result that tonic extension of the lower extremities was produced for the first five or six minutes of the scheduled ten minute treatment. As the current was reduced, vigorous clonic movements usually occurred. It at once became evident that peripheral stimulation of this type was markedly effective in regulating the respiratory rate and that arousal from anesthesia was produced. Also it was quite noticeable that peripheral stimulation produced clonic muscular movements of much larger amplitude than cranial stimulation. Some of the patients of the trial group complained of muscle cramps at the end of stimulation and when examined several hours later were limping and showing muscle soreness with movement and pressure. Yet all five patients were obviously happy and euphoric in somewhat of a contrast to their previous moods. All appeared pleased with the treatments in spite of sore muscles.

Anesthesia was not used with the trials of peripheral stimulation on ourselves. Various electrode placements on the legs were tried. In applying currents to ourselves, however, we started at zero and worked cautiously upward. Also, an ammeter was attached to the machine which allowed a more precise adjustment of current. With each upward

turn of the current, a scratchy, needlelike burning of the skin at electrode sites was felt for a short time. From about 0.5 milliamps and above, throbbing sensations could be felt in muscles in synchrony with clonus. By taking ten to fifteen minutes to increase the current progressively, we were able to tolerate up to 8.0 milliamps. As muscles appeared to go into tonic spasm, the discomfort became painfully intolerable. During and following the several applications of current, some of which lasted twenty minutes, we experienced a definitely pleasurable affect. This was in dramatic contrast to that experienced when we gave ourselves unidirectional currents through bifrontal, biparietal and occipital electrode placements. Although no more painful than the leg applications, the maximum current which could be tolerated in this manner was 3.5 milliamps. Very disagreeable affective depressions were produced from these cranially applied currents. Subjectively, we felt dejected and slightly nauseated and to our colleagues we looked physically ill. The disagreeable apathetic states were quickly overcome, however, by a few minutes application of current peripherally which was then continued for approximately fifteen minutes.

On the basis of the five single trials on anesthetized patients and our personal experiences, it appeared that a decided difference in mood resulted from unidirectional currents applied through head electrode placements and those given through peripheral electrodes. Likewise, it was thought that post-treatment muscle cramps were probably associated with the tonic contractions produced by the upper ranges of current and by the electrode placement on the calves. Reiter's button type electrodes were associated with second degree burns over the calves in two instances. For these reasons, the idea of paralleling the current strengths of Alexander's nonconvulsive technique for purposes of comparison was given up and the following method was devised.

Method

Two cloth-covered electrodes, 3½ by 5 centimeters, are dipped in saline and secured on the anteromedial aspect of each leg, approximately 5 centimeters below the tibial tuberosities. These are connected with a divided wire which is plugged into the negative position of a Reiter CW-47B or C Electrostimulator. A third wet electrode, 3½ by 10 centimeters, is secured over the patient's lumbosacral region and connected to the positive outlet of the Reiter machine. With the patient lying on his back on top of a bed, anesthesia is accomplished by 2% sodium pentothal intravenously. A satisfactory depth of anesthesia is determined in a manner similar to the Impastato technique in nonconvulsive electroshock; the unidirectional current from position I is gradually increased until 2½ milliamperes will be tolerated by the patient. Rhythmical movements of the toes usually occur as the current is increased to 0.5 M.A. and progressively includes the muscles of the legs, thighs and the dorsal musculature of the back as the current is increased. Clonic movements usually cease with the muscles rigidly contracted and legs held in extension as currents amount to 6 to 12 M.A. and more. After the patient has been adequately anesthetized, current is raised to a point just beyond that at which respiration may be stopped. The current is held there for 40 to 60 seconds until respiration breaks through at which point the amperage is adjusted downwards. If respiration does not completely stop with maximum stimulation of 20 M.A. or if it does not return within sixty seconds, the amount of current is nevertheless decreased to the point at which satisfactory hyperpnea is obtained. As breathing is controlled the amount of current is regulated to obtain maximum clonic muscular movements and to avoid tonic contractions. The most satisfactory movements are usually obtained from 5 to 8 M.A. Stimulation is contined at this level until the patient starts to arouse and then it is slightly decreased. Downward adjustments are made as often as necessary for the patient to tolerate the treatment comfortably for ten minutes. If the patient is not awake at the end of ten minutes stimulation is continued until he regains consciousness.

Case Material

Although it was originally presumed that peripheral electrical stimulation might act clinically in a manner similar to nonconvul-

sive electroshock, it was decided to study patients with both central sympathetic hyporeactivity and hyperreactivity to the Funkenstein test. For the purposes of this investigation, hyperreactivity is arbitrarily defined as an elevation of 10 points above the resting systolic blood pressure level subsequent to mecholyl-induced hypotension and/or blood pressure elevation of 50 points or more following .025 mgms of adrenalin. Central sympathetic hyporeactivity is defined as a persistence of a ten point hypotensive reaction to mecholyl beyond 12 minutes from the time of injection. Fifteen patients recently admitted to Northern State Hospital were selected who met these criteria. Nine demonstrated hyperreactivity and six demonstrated hyporeactivity to the Funkenstein test. The nine hyperreactive patients were diagnosed as follows: Paranoid schizophrenia, two; catatonic schizophrenia, two; schizophrenia mixed type, one; psychoneurosis, one; involutional psychosis, paranoid type, one; and manic depressive psychosis, depressed type, two. The six hyporeactive patients had the diagnoses of: Paranoid schizophrenia, one; catatonic schizophrenia, one; and involutional melancholia, four. Only two patients of this study, E. F. and R. R., who were considered treatment failures, had received previous physiological treatment and they had received no treatment for over one month prior to peripheral electric stimulation. With the exception of the first patient who received ten treatments, twenty treatments were given to each of the group of fifteen.

Results

Other than tender muscles for the first few days of treatment no complications or complaints were noted. Peripheral electrical stimulation was given on wards where active programs of convulsive electroshock, nonconvulsive electroshock and insulin coma therapies were in operation. Thus, patients received no special attention in the application of treatment. Peripheral stimulation was scheduled about three times per week and it was noted that the patients were much more active, cheerful and friendly on treatment days. In some patients it was possible to give stimulation without anesthesia as their courses progressed. In these, however, currents seldom exceeded 5 M.A.

Of the nine hyperreactive patients, four received no additional treatment and have been released from the hospital. Five received additional treatment in the form of combined convulsive-nonconvulsive electroshock therapy in three instances and insulin coma and additional peripheral stimulation in one case each. The present status of the nine hyperreactive patients shows two remaining in the hospital and seven released. Of the six hyporeactive patients, two improved with no additional treatment although in both cases previous treatment had been given with no apparent improvement. None of the four hyporeactive patients without previous treatment was improved by peripheral electrical stimulation. In three of these cases, convulsive electroshock therapy was given with prompt favorable results. No additional treatment of the fourth case was possible as she was deported to California. At this time, three to eight months after the completion of treatment of the last patient in the series of fifteen, we find that twelve have shown sufficient improvement to leave the hospital.

From the results of a preliminary study of peripheral electrical stimulation of fifteen patients it appears that the Funkenstein examination is useful in selecting those who might benefit from the method. As with nonconvulsive electroshock, it is seen that patients with hyporeactive central sympathetic centers do not appear to respond favorably whereas patients with central sympathetic hyperactivity are significantly benefited.

Discussion

Peripheral electrical stimulation as used in this study is essentially intense afferent input in the form of repeated, continuing proprioceptive and nociceptive impulses. In formulating a hypothesis to explain the manner in which such afferent input might influence behavioral abnormalities associated with central autonomic dysfunction, we start by referring to the contributions to the physiology of awareness which have been made by Magoun,[8,9,10] and his colleagues. These

TABLE 1

Results of Peripheral Electrical Stimulation in Fifteen Patients

Patient	Age	Diagnosis	Previous Treatment	Funkenstein Test	Course of Peripheral Electrical Stimulation		Immediate Post-treatment Results	Subsequent Treatment	Present Status
H.R.	34	Schizophrenia, catatonic type	None	Hyperreactivity 112-128 M 112-168 A	10-7-54	11-3-54	Improved	None	1-21-55 Paroled
E.V.D.	53	Involutional psychosis, paranoid	None	Hyperreactivity 100-130 M 100-160 A	8-19-54	9-24-54	Improved	20 Peripheral Electrical Stimulations 10-12-54 to 11-10-54	Paroled 12-5-54
W.L.	18	Psychoneurosis Conversion hysteria	None	Hyperreactivity 90-98 M 90-162 A	7-7-54	8-16-54	Improved	None	Discharged 11-8-54
E.F. (male	38	Schizophrenia, catatonic type	12 convulsive electroshock 6-11-54 : 7-10-54 6 convulsive electroshock 7-20-54 : 7-31-54 12 convulsive-nonconvulsive 8-12 : 9-13-54	Hyporeactivity 106-94 M 106-135 A	10-25-54	11-19-54	Improved	None	Paroled 3-11-55
E.H.	27	Schizophrenia, mixed type	None	Hyperreactivity 108-118 M 108-142 A	11-15-54	12-14-54	Improved	None	Paroled 2-11-54
R R.	65	Involutional melancholia	10 convulsive electroshock 5-13-54 : 5-24-54 18 convulsive-nonconvulsive 6-21-54 : 7-13-54	Hyporeactivity 160-142 M	8-26-54	9-21-54	Improved	None	Paroled 11-1-54
S.S.	35	Manic depressive psychosis, depressed	None	Hyperreactivity 104-98 M 104-169 A	7-1-54	8-9-54	Unimproved	34 -convulsive-nonconvulsive electroshock 9-3-54 : 11-11-54	Discharged 2-1-55
A.G.	27	Schizophrenia, catatonic type	None	Hyperreactivity 100-120 M 100-162 A	10-21-54	11-24-54	Unimproved	24 convulsive-nonconvulsive electroshock 12-6-54 : 1-25-55	Discharged 3-18-55
V.S.	30	Schizophrenia, paranoid type	None	Hyperreactivity 100-120 M 100-152 A	9-13-54	10-12-54	Unimproved	Insulin coma 11-6-54 : 2-1-55	Unimproved in hospital
A.C.	28	Schizophrenia, paranoid type	None	Hyperreactivity 100-118 M 100-160 A	8-10-54	9-4-54	Unimproved	14 convulsive-nonconvulsive electroshock 10-5-54 : 11-1-54	Unimproved in hospital
C.H.	46	Schizophrenia, paranoid type	None	Hyporeactivity 160-134 M	7-20-54	8-16-54	Unimproved	12 convulsive electroshock 9-9-54 : 9-29-54 8 additional 10-5-54 : 10-18-54	Discharged 12-19-54
M.McC.	45	Involutional Melancholia	None	Hyporeactivity 92-80 M	6-30-54	8-9-54	Unimproved	Deported to California 8-11-54	Unimproved in a California State Hospital
C.H.	59	Involutional Melancholia	None	Hyporeactivity 170-146 M	7-29-54	8-26-54	Unimproved	12 convulsive electroshock 9-9-54 : 9-29-54 5 additional 10-19-54 : 11-1-54	Paroled 12-12-54
H.J.	54	Involutional Melancholia	None	Hyporeactivity 148-134 M	8-6-54	9-7-54	Unimproved	4 convulsive electroshock 1$-5-54 : 10-12-54	Discharged 12-4-54
E.C.	38	Manic depressive psychosis, depressed type	None	Hyperreactivity 98-104 M 98-164 A	6-10-54	6-30-54	Improved	None	Paroled 8-20-54

workers have shown that various stimuli are capable of producing an arousal reaction which is associated with generalized cortical activity and simultaneous excitation of what they have termed the reticular activating system. These responses are nonspecific as to the modality of stimulation and have a longer latency period than the localized cortical potentials evoked by specific sensory stimuli. Moreover, the cortical and reticular responses associated with arousal can be depressed and abolished by deep barbiturate anesthesia during which specific sensory stimuli continue to produce localized cortical responses. The presence of the two central sensory systems is likewise demonstrated in animals with lateral or medial brain stem lesions. In animals with lesions of the classical lemniscal pathways, auditory stimuli succeed in producing arousal from sleep. Lesions of the medial brain stem tegmentum, however, result in states resembling coma from which the animals can be temporarily aroused with difficulty or in some cases not at all. By placing unilateral lesions in the hypothalamus, Koella and Gellhorn[11] have demonstrated that this region is largely involved in arousal to nocioceptive stimuli. In such preparations they noted that generalized cortical activity associated with arousal was confined to the side of the intact hypothalamus. Gellhorn[12] has reviewed the considerable neurophysiological work of recent years relating to consciousness and perception and concludes that whereas awareness depends upon the reticulo-hypothalamic-cortical system, perception involves an interaction of this system and impulses reaching the cerebral cortex via the specific sensory system. Gellhorn states, "Although the site of this interaction has not yet been determined, the interaction appears in an intensification of the cortical sensory response and also in an increase of the cortical area from which it may be recorded. These phenomena may be related to the quantitative alteraction of sensations under the influence of emotion."

Hebb[13] has demonstrated that prolonged decreases of afferent input result in marked behavioral abnormalities in animals and in man. In some cases he has succeeded in producing hallucinatory states by the mere process of reducing afferent input to a minimum for prolonged periods. In these cases the performance of the subjects as students was impaired for several days following restoration of normal activity.

It appears logical, therefore, to suggest that peripheral electrical stimulation successfully improves mentally ill patients with central sympathetic hyperreactivity by profoundly influencing the physiological mechanisms underlying perception. It has been clinically observed that these patients show many subtle alterations in perception and some are grossly confused and disoriented. This is in harmony with clinical experience which shows that confused excitement states inadvertently produced by convulsive electroshock are promptly overcome with nonconvulsive electroshock with a concomitant shift in the Funkenstein response from hyperreactivity to hyporeactivity. As the improvement in perception with nonconvulsive electroshock is probably brought about by stimulation of peripheral cranial nerves, it is suggested that the same effect is produced by peripheral electrical stimulation as used in this study. Stating the concept differently, it might be said that in some mental illnesses afferent input of ordinary intensities is insufficient to maintain undistorted perception and adequately functioning central autonomic homeostasis. Extraordinary afferent input as administered by peripheral electrical stimulation probably improves abnormal mental states by acutely influencing the previously described physiological mechanisms mediating levels of awareness and perception. Regardless of theoretical speculations as to the mode of action of peripheral electrical stimulation, the fact remains that such treatment does produce marked changes in the mood and behavior of certain mentally ill patients.

On the basis of this preliminary study of 15 patients and parallel studies at Northern State Hospital of peripheral electrical stimulation in insulin coma,[14,15] it has been decided to investigate this method of treatment further. Three modifications have been made, however. First, only patients with central sympathetic hyperreactivity are being chosen for stimulation. Second, patients are now being anesthetized to the point that 20 M.A.

of current are tolerated without signs of voluntary movement. This level of barbiturate anesthesia has been allowing high current strengths to be given for most of the treatment which customarily lasts about twenty minutes. Third, if any of those patients now under study do not improve with twenty treatments the courses will be extended.

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A Year's Experience With Frenquel In Clinical and Experimental Schizophrenic Psychoses

HOWARD D. FABING, M.D., and J. ROBERT HAWKINS, M.D.
Cincinnati, Ohio

For the past two and a half years we have been interested in certain piperidyl compounds as possible therapeutic agents in neurology and psychiatry. The first of these compounds studied clinically[1] was alpha-(2-piperidyl) benzhydrol hydrochloride, or Meratran, which has proved to be a central nervous system stimulant without concomitant effects on the autonomic apparatus. The unique clinical properties of this compound, plus the finding that its site of action appears to be, at least in part, in the upper brain stem tegmentum[2] and the septal area[3] prompted the thought that other compounds of this general configuration might also be of value as therapeutic agents in disorders of the central nervous system.

Frenquel*, a bitter white crystalline substance, the gamma isomer of Meratran, is the first of its congeners to be investigated clinically. The only difference in the two compounds is that the NH radical is moved from the 2-position to the 4-position in the piperidyl ring. This small change in structure causes a complete change in the pharmacological action of the parent compound. Frenquel is not a central stimulant, as is Meratran, but is rather an antagonist of cerebral stimulants in the mouse,[4] and is of extremely low toxicity.

Clinical trial of this compound by oral administration was begun in Christ Hospital, Cincinnati, and has continued throughout the

From the Department of Neurology, Christ Hospital, Cincinnati.

Read before The Society of Biological Psychiatry, Chicago, Illinois, June 12, 1955.

past year. This report concerns itself with a review of our experience with Frenquel in clinical and experimental schizophrenic psychoses during that period.

Encouraging, though inconsistent, results in some of our early clinical cases prompted us to test the use of Frenquel as a premedication to block model LSD-25 and mescaline psychoses. Two healthy subjects, who developed typical psychoses after ingesting 100 micrograms LSD-25, failed to develop them a week later after premedication with Frenquel during the intervening week.[5] In a third unprotected test five weeks later, the LSD-25 psychosis was brought to an abrupt end in one of the subjects by the intravenous injection of Frenquel.[6] Further observations on healthy subjects disclosed that they developed no LSD-25 psychosis, or only fragments thereof, on doses of the blocking agent varying from 10 to 50 mg. daily for one prior week, or on doses of 100 mg. daily for two prior days. Four observations suggest that model psychoses produced by mescaline sulphate can be controlled in the same fashion[7] as those induced by LSD-25. Recently we attempted to study the blocking effect of Frenquel on model psychotic reactions produced by the ingestion of 45-60 mg. of pyrahexyl,[8] a synthetic compound closely related to tetrahydrocannabinol, the active principle of canabis. The results were not clear-cut, and further observations will be carried out in other cannabis experiments, but our preliminary conclusion is that Frenquel fails to block this type of model psychosis. As other hallucinogenic substances[9] become available to us, we plan to study Frenquel's possible blocking effect on the experimental psychoses they may produce.

Trial of Frenquel in clinical disorders has involved a total of 115 cases during the past year. These have all been private patients under our direct observation and care in hospital and office practise. We have followed these patients together, on a day-to-day basis.

We have done our own social work on these patients, and we have had the help of adequate psychiatric nursing care throughout the study. Some of the patients have literally grown up with us in our practise, in that we have observed them periodically for as long as 20 years before Frenquel was tried therapeutically. In a patient sample of this type one has the assistance of interested, and even dedicated, relatives who are able to enlarge upon the clinician's observations as well. Economically this group runs the full gamut from the well-to-do and the well educated to the very poor who have been denied most of the advantages of formal education. Socially and culturally they extend from the sophisticated urban dweller to the one-horse hillside farmer who has not often seen many buildings bigger than the county courthouse in his lifetime. Ethnically they are composed of the mixture which makes up the Ohio Valley peoples of Kentucky, West Virginia, Indiana and Ohio.

Although we have studied Frenquel in the treatment of a great number of neuropsychiatric disorders, we are impressed with the fact that it seems to be of therapeutic value only in patients who exhibit symptoms of the schizophrenic reaction pattern, and inconsistently in these. Any attempt to develop a measuring scale for improvement in this large and heterogenous group of sick people is fraught with great difficulty. How long has the patient been ill? How crippling has the illness been? What special pathology may be contributing to the particular schizophrenic process under study? What social and interpersonal factors may be present to hasten or retard recovery? What ancillary therapies may have contributed to the result? What criteria are being used to define slight, moderate, marked or full improvement? How long are the results likely to hold up? These and many other questions plague anybody who attempts to appraise the efficiency of a therapeutic agent in schizophrenic disorders.

In order to cope with some of these questions, we have divided the patients under study into the categories of acute and chronic schizophrenia, alcoholic hallucinosis, senile dissociation states, and other disorders. An interesting group of patients with post-operative confusion is added. Practically none of our patients have been as crippled by long-term schizophrenia as those one meets on the back wards of state hospitals, because if they were that sick any appreciable length of time, they would have

gravitated to such wards for the most part, since this sample is composed of a cross-section of the populace. Where ancillary therapies have been used, we have indicated them. No special psychotherapy has been employed in the treatment of these patients beyond that to be found in the usual doctor-patient relationship. We have confined our measurement of improvement to the single criterion of return to full social and vocational reintegration.

Acute Schizophrenia

These 14 patients were all ill less than five months. All were hospitalized as acute emergencies, all were hallucinated and/or seriously deluded, all exhibited a dissociation of the continuity of the thought process, and all were dissociated from the reality situation. Nine were overactive, five were withdrawn. The daily Frenquel dosage will be seen to be quite variable. This reflects our groping by the trial and error method toward an understanding of the effective dosage range. See Table I.

Five of the 14 patients lost their schizophrenic disorder within one to three days on Frenquel alone. Three others showed definite improvement on Frenquel, but of less dramatic suddenness, and with residual depressive features. Short courses of electroconvulsive therapy completed their recovery. Another patient was placed on both Frenquel and chlorpromazine simultaneously by error after emergency admission. He cleared mentally in three days, but the relative effect of each of the two drugs remains a mystery. Five others are considered Frenquel failures because they did not begin to respond until E.C.T. was added. Twelve are at their regular pursuits. None has had recurrences over periods as long as eleven months. All are maintained on Frenquel. One, the dental technician, abandoned her maintenance dose of the drug, and had a recurrence of her wild acute schizophrenic illness nine days later. This cleared up rapidly a second time when the drug was reapplied.

Chronic Schizophrenia

This group comprises 34 patients. They range in age from an eleven year old juvenile to three women of sixty years of age. Duration of illness has varied from one to twenty-five years. Some of these patients would have been placed in state hospitals had it not been for the determination of relatives to keep them at home. Only three of the men were regularly employed, one as a business executive whose paranoid state had required his associates to adjust his duties downward repeatedly, one as a linotype operator who was about to be dismissed for absenteeism and poor workmanship, and the third as a marginal farmer. None of the women in the group was able to carry out the duties of a housewife successfully. One of us (H.F.) brought one of the resistant patients into his home as a maid for two months to observe her more closely and to provide a more stable environment. The experiment was a failure. They fell into all of the Kraepelinian subgroupings clinically, with the paranoid variety predominating by

TABLE I

ACUTE SCHIZOPHRENIA

Case	Age	Sex	Type	Duration Weeks	Maximum Dose, mg/day	Other Treatm.	Result	Adjustment
1.	30	F	S-Affective	1½	70	ECT	+	Housewife
2	46	F	Paranoid	8	300	——	+	Bus. Executive
3.	43	F	Paranoid	6	80	——	+	Housewife
4.	35	F	Paranoid	6	15	——	+	Dental Tech.
5.	18	M	Catatonic	12	45	ECT	+	Student
6.	40	F	Paranoid	1	20	——	+	Housewife
7.	35	F	Paranoid	1	300	ECT	+	Housewife
8.	64	M	Catatonic	2	20	——	+	Writer
9.	50	M	Recurrent S-Affective	4	300	Thor	+	Composer
10.	29	F	Recurrent Paranoid	8	100	ECT	0	Ill at Home
11.	23	F	Post-Partum	4	200	ECT	0	Housewife
12.	19	M	Paranoid	1	300	ECT	0	Truck Driver
13.	27	F	Paranoid	6	400	ECT	0	Hospitalized
14.	29	F	Recurrent Paranoid	20	400	Thor ECT	0	Housewife

TABLE II
CHRONIC SCHIZOPHRENIA

Treatment	Good Result Full Adjustment	Poor Result Dependent
Frenquel only	8	11
Frenquel + ECT	3	4
Frenquel + Chlorpromazine	3	1
Frenquel + Reserpine	0	1
Frenquel, Chlorpromazine and ECT	2	1
TOTAL	16	18

far. Some improved on Frenquel alone, others did not. The addition of E.C.T. to Frenquel, the addition of chlorpromazine and reserpine to Frenquel, and the combination of Frenquel, chlorpromazine and E.C.T. have all been tried in this group. Results are tabulated in Table II.

If the rigid criterion of full social and vocational adjustment is kept in mind as our measuring stick for therapeutic effectiveness, this record of a return to normal living habits in almost half of these patients is heartening, and is definitely beyond our expectation in a similar group of patients before Frenquel was available to us. Since we have known and treated a large number of these patients by other means on former occasions, the therapeutic result gains increased impressiveness as we review individual case records.

Case Report

Our first case with Frenquel was a chronic schizophrenic.[10] A 19 year old girl became hostile toward parental domination in 1950 and demanded transfer to a college far from home in 1951. She became acutely hallucinated and deluded in January, 1952, and was removed to hospital under our care as an emergency. An arduous four months of E C.T. plus insulin coma therapy yielded enough betterment to permit her to return home. During the next two years she made two failures at college and two more at jobs. Her hostility toward her family mounted, and by March, 1954, she had almost made herself a full-time prisoner in her room. In June, 1954, she erupted with an angry, aggressive excitement which required emergency admission to hospital once more, where she had to be tied to her bed or locked in her room. This was our first experience with Frenquel, and we began with milligram doses orally. She quieted down, and we raised her dose gingerly. She became more tractable and more communicative.

She told of her frightening visual hallucinations, such as walking arm-in-arm with corpses who had worms crawling out of their cheeks, of being enclosed in a giant clam shell, and of walking through beautiful formal gardens with her lover who was—she did not know who he was because he changed faces and bodies too quickly. She told of auditory hallucinations of beautiful music, of terrible music, of beautiful poems read to her between shouts calling her a slut and a whore. She began to eat well and to gain in weight and color. We raised the dose of Frenquel and reality began to return as the hallucinatory phenomena faded. She discussed clothes with the nurses in an almost professional way. Her work in occupational therapy disclosed a real flair for form and materials. Five weeks after admission, she attended a performance of *La Boheme* one night, hummed through all the good arias, discussed the plot critically and behaved like any other patron in the opera pavilion.

In the ensuing nine months she has been at home. She enjoyed running a toy department in a neighborhood store during the Christmas shopping season, and then got a job as a secretary in a modelling establishment. She helps dress the models and arrange fashion shows, and acts as a model herself on occasion. She reports that she and her boss get along well together, and she enjoys her work fully. Her mother tells us that except for occasional arguments, usually over matters of taste in decoration and dress, the patient is again a thoroughly integrated member of the household. She has tried to stop her maintenance dose of Frenquel (50 mg. daily) on two occasions, but finds that she soon begins to "get muddled," and has resigned herself to the nightly ingestion of the tablets. At the last visit she was asked to increase the dose to 100 mg. nightly in the hope that she and her mother might live in more complete amity despite their differences in taste.

A 48 year old linotype operator is exemplary of the effect of Frenquel plus clohpromazine. He was discharged from the Navy in 1944 with a diagnosis of schizophrenia. He has been plagued by almost continuous voices which call him dirty names since that time. His whole life has been occupied by an attempt to figure out the source of these voices. They waken him at night and he rushes to the window, throws it open, and curses back at them. At other times, he rushes out on the porch in his pajamas and shouts defiance at his tormentors. When the neighbors begin to complain too much about his disturbance of the peace, his wife wheedles him into taking a short course of E.C.T., which he abandons as quickly as the voices start to subside. This pattern has been repeated five times in the last 10 years. There is much about schizophrenia which is baffling, to be sure, but this man's ability to operate a linotype machine despite such a handicap is beyond our comprehension. During one of his periods of exacerbation, chlorpromazine was prescribed but he abandoned its use because he thought it made him worse. Nine months ago he

was given Frenquel orally. On a dose of 100 mg. daily the auditory hallucinations subsided in frequency and urgency but did not disappear. Then chlorpromazine was added in the same quantity. For the past four months he has been entirely free of his hallucinatory experiences, has worked steadily, and has begun to expand his social horizons.

A thirty year old housewife typifies a good result in a patient who received Frenquel, chlorpromazine and E.C.T. Three years ago she lost interest in her home and her children, thought her head had grown to the size of a large balloon, and began to hear tiny voices coming from her occiput or from a point above and behind her right ear. They were alternately accusatory and pleasant. Dissociation of the continuity of thought became disabling, and she lost her skills as a housewife. She sent her children to the farm of her parents in Indiana because she felt that she could no longer carry on the functions of a mother. Her husband gradually took over the cooking, laundering and marketing as she sat long hours staring into space, living almost exclusively in her autistic other-worldly world. At the insistence of her family physician, she finally submitted to hospitalization. At first she was almost incapable of communication, but as her daily dose of Frenquel reached 100 mg. she became more animated and better able to tell us of her difficulties. The voices and the distortion of head size continued, but her autistic withdrawal was less marked. When chlorpromazine was added in a dose of 100 mg. daily the auditory hallucinations faded but did not vanish, and she lost the idea that her head was as big as a balloon. She became depressed however, and began to cry a great deal, saying that she was a failure, that she would never be able to measure up to being a mother and a home-maker. Six E.C.T. treatments were given. At the end of that time her mood level was elevated and the schizophrenic process appeared to have abated. She went home after some urging, and within four weeks brought her children back into the home. She has gained 25 pounds and her husband reports that for the past two months he has had the girl he married for a wife once more. She continues to take 100 mg. of both Frenquel and chlorpromazine daily.

None of the patients who have obtained full social and vocational adjustment have regressed in this short period. Two patients who were partially improved seem to have had an increment of schizophrenic dissociation, however, despite the continuation of therapy. Insight in the chronic group is less good, on the whole, and these patients are more likely to abandon maintenance treatment unless urged to continue it.

It is fascinating to watch the process of recovery as it occurs in the more successful chronic cases. A mind which has been filled with the preoccupations of autistic thoughts for a long time apparently needs to go through a period of adjusting to their absence. This adjustment is not as evident in schizophrenic patients who receive benefit from the shock therapies as it is in those who are relieved by drug. One patient reported that her mind felt like an empty bucket when her hallucinations were relieved, and she could not really tell us how she was getting along until she filled the bucket once more "with everyday things."

Rinaldi, Rudy, and Himwich[11] have also reported on the therapeutic effect of Frenquel in chronic schizophrenia recently. Using a double-blind technique, they found that 21 of 39 chronically ill institutionalized schizophrenics received measurable benefit from the oral administration of 20 mg. of the drug daily during an eight week observation period. They are repeating their experiment with larger doses at the present time.

Alcoholic Psychoses

Unfortunately this group is too small to be of any value beyond indicating that psychiatric disorders having an alcoholic etiology are worthy of trial with the drug. Our experience in this group is summarized in Table III.

Case Reports

The first patient with auditory hallucinosis was a salesman who began to hear accusatory voices one night a year before admission while he was sitting at a bar. He thought the customer next to him had begun to call him dirty names, and invited him outside. The fellow-drinker complied, and gave our patient a thorough beating. There followed a year of his trying to find hidden loud speakers in his home, his car, his office, etc., to determine the source of the voices. He began to avoid taverns, movie theatres, phone booths and even customers' offices where the voices had been particularly upsetting. He recovered in a few days on Frenquel orally, and when he discovered that alcohol was the cause of his year of torment he swore off drinking. He is maintained on Frenquel at 50 mg. t.i.d. On occasion he fears that the voices will return, but he has had no recurrence.

The second patient, a female wine-bibber, came to us early in our experience with Frenquel. The accusatory profane voices did not abate on the low dose of 20 mg. daily. In retrospect, we feel that the result might have been better if the dose had been higher.

The third case, an acute harrowing experience in a socially prominent young matron who has been a heavy drinker since her college days, came to an

abrupt end within 24 hours of the administration of three doses of 10 mg. of the drug. She wrote out her subjective account of the episode in which the entire citizenry of her suburban town gathered on her lawn to cast innumerable votes over the proposition of having her banished from the town. After she was banished she seemed to die, and then listened to a repeated intoning of her funeral oration. Although she determined not to do so, she has resumed her drinking pattern despite her use of Frenquel in doses up to 400 mg. daily for a period of two months. After that time, she abandoned its use. The fourth case was in a woman who denied that she drank excessively, despite her husband's testimony to the contrary. Her hallucinosis cleared up but she became depressed. E.C.T. was added and she appeared fully recovered when she returned home. She soon quit taking her maintenance dose of Frenquel, and her family physician reports that she has resumed her drinking pattern.

The paranoid reaction arose in another socially prominent woman, and assumed the common pattern of delusions of infidelity on the part of her husband. This persisted despite two years of intensive psychotherapy. She moved to Cincinnati and as soon as she and her husband met new people there, she added a fresh group of women to her husband's list of paramours. On 200 mg. Frenquel daily this whole pattern of thought has abated, and she has cut her alcohol consumption down appreciably. This single result is impressive, but observations on a much larger group of these cases for a longer period will be necessary before one dares to become optimistic about the value of Frenquel in alcoholic paranoia.

We reported that a surgical patient with delirium tremens experienced cessation of his hallucinations of multi-colored fluorescent bugs crawling on the ceiling within 30 minutes after intravenous injection of 100 mg. of Frenquel in a previous communication.[12] Unfortunately, this patient developed a bowel strangulation seven days later and died, so that our observation is an incomplete one. Despite diligent search, we have found no further cases of this type for study as yet.

Senile Dissociation Syndromes

Although this series is also small, we find encouragement for further study in our results. The periodic psychotic episodes which occur in older people as a complication of the organic brain syndromes constitute a large problem in geriatric practice. Although it has been able to do nothing for the memory defect, the flattened affect, the inertia nor the neurological accompaniments of these disorders, we have been impressed by the ability of Frenquel to relieve noisy confusion, paranoid fears and hallucinatory symptoms in these patients. The nurses have been particularly impressed with the improvement gained in this group. These patients account for a great many accidents within a hospital, and often disrupt the peace of the night hours. Furthermore, as physicians we are charged with the care of the dying, and if we can make the last days of a noisy moribund patient more peaceful, we have performed our task in a better fashion. See Table IV.

One older lady was relieved in great measure of her fear that a gang was after her. One rich man was relieved of the fear that a former wife was going to put him in jail and take all his money away. Two older men who had kept up a noisy uproar throughout the day and night as soon as the effect of their sedatives wore off, became quiet and cooperative and were relieved of restraints after receiving large doses of Frenquel. Both died peaceably within a month. The aunt of a nurse was relieved of voices telling her to run away. She has improved to such an extent that plans to probate her have been cancelled. A man who was plagued by the conviction that bugs were crawling over him, and in whom no disease process to account for his formication could be found, was relieved by small doses of Frenquel.

Other Disorders

In the course of this exploratory survey of Frenquel's possible therapeutic action in psychiatric and neurological disorders, the drug

TABLE III

ALCOHOLIC PSYCHOSES

Case	Age	Sex	Type	Duration	Dose, mg/day	Result
A.M.	40	M	Auditory Hallucinosis	1 yr.	150	Full Recovery
E K.	47	F	Auditory Hallucinosis	5 yrs.	20	Failure
A.C.	35	F	Auditory Hallucinosis	1 wk.	20	Recovery — Rapid
M S.	42	F	Auditory Hallucinosis	6 yrs.	80+ECT	Improved, but Inadequate Follow-up
M.R.	43	F	Paranoid Reaction	2 yrs.	200	Full Recovery
J.E.	50	M	Delirium Tremens	3 days	100 I.V. 300 orally	Recovery — Rapid Death later — Other cause.

TABLE IV
SENILE DISSOCIATION STATES

Case	Age	Sex	Type	Dose mg/day	Result
E.P.	75	F	Paranoid	.5	Relieved partially
E.S.	64	M	Paranoid	20	Relieved
W.G.	77	M	Noisy confusion	400	Relieved, died later, coronary
E.H.	75	M	Noisy confusion	400	Relieved, died later, diabetic gangrene
M.B.	72	F	Hallucinated	200	Relieved
J.B.	66	M	Somatic Hallucinations	15	Relieved
J.F.	77	M	Disorientation	100	Failure, cortical atrophy

has been tried in a variety of clinical conditions without benefit. These are recorded in Table V.

TABLE V
OTHER CONDITIONS

Type	Cases	Result
Agitated Melancholia	4	Failure
Anxiety, Chronic	2	Failure
Anxiety, Phobic (Thunderstorms)	1	Failure
Liver Disease, Jaundice	2	Failure
Obsessive-Ruminative	2	Failure
Obsessive-Compulsive (Handwashing)	2	Failure
Alzheimer's Disease	5	Failure
Psychomotor Fits	1	Failure
Morphine Addict	1	Failure
Rheumatic Encephalopathy	1	Failure
Multiple Sclerosis (With euphoria)	1	Failure
Porphyria (Acute intermittent)	2	*
Diabetic Neuropathy	1	*

*See text.

Manic Depressive, Depressed	1	Failure
Melancholia	2	Failure

The list is self-explanatory, and requires no discussion. It emphasizes to us the narrow specificity of Frenquel's therapeutic action. The young lady who has rheumatic encephalopathy is hebephrenic, and has seizures which are controlled by dilantin. Frenquel alone and Frenquel plus chlorpromazine have failed to alter her hebephrenic pattern. The porphyria patients are both women. Porphobilinogen has been found repeatedly in their urine. The younger patient has had only abdominal and peripheral neuritic symptoms, and has never had a psychotic episode. During the two months of its use, Frenquel has relieved her abdominal symptoms greatly in daily doses of 200 mg. and she has gained ten pounds in weight, but the peripheral neuropathy has not changed. The older patient has had seizures, abdominal pain and profound disorientation plus auditory and visual hallucinations. On 400 mg. Frenquel daily there has been no change whatever in her mental status, but she, too, has complained far less of abdominal distress. During the two months she has been under treatment, there have been no seizures, but these have always been infrequent. The man with diabetic neuropathy claims that he is better in that the paraesthesias are of a different and less painful quality. His neurological status remains unchanged, and we are inclined to doubt the validity of his report at this time.

Post-operative Confusion

A curious coincidence which has led us into a new line of inquiry occurred in February, 1955.[13] The father-in-law of one of us (H.F.) had undergone a prostatectomy and he developed a confusional state on the second post-operative day. He is a physician and an articulate man. He told of sensations of levitation, of visual and haptic hallucinations, of a feeling of drifting into a wierd world dissociated from the real one, and of the sensation of fear and foreboding which accompanied it. The similarity between his stream of talk and that of LSD-25 and mescaline subjects was striking, and prompted us to give him 50 mg. Frenquel intravenously. He described the progressive amelioration of his dissociated mental state during the next half hour. The medication was continued orally during the remainder of his hospital stay, and his course was un-

TABLE VI
POST-OPERATIVE CONFUSION

Procedure	Cases	Relieved	Died
Prostatectomy, suprapubic	7	6	1
Prostatectomy, Transurethral	4	4	–
Hip Fracture, Pinned	6	6	–
Cystotomy	2	2	–
Cataract	2	2	–
Pancreatic Abscess	1	1	–
Strangulated Hernia	1	1	–
Bowel Resection	1	1	–
Appendectomy	1	1	–
Gunshot Wound, Legs (Pulm. Fat Embolus)	1	1	–

eventful thereafter. With the cooperation of our surgical colleagues, we have initiated a study of post-operative confusional states at Christ Hospital following this experience. Table VI summarizes our results to date.

These patients have ranged in age from 53 to 89 years. Genitourinary surgery and fractures of the neck of the femur account for the bulk of these patients, as every surgical nurse knows. Careful clinical study of these patients discloses that this type of "confusion" is strikingly similar to an acute schizophrenic dissociation. Auditory and visual hallucinations, paranoid productions, disorientation, psychomotor overactivity, mood disturbances, fear reactions and dissociation of thought are all compounded to produce what we describe loosely as post-operative confusion.

It is the rule that the development of these psychoses is delayed for at least 24 hours after the surgical procedure. In hip fractures there is a similar lag period between the trauma and the development of the psychosis, if our small series can be relied upon. The type of anaesthesia used is apparently not significant, nor is the presence of hypertension, arteriosclerosis, myocardial weakness nor nitrogen retention, despite the fact that post-operative confusion is prone to occur in the older age groups where such disorders are met frequently. The cause of these reactions is unknown. We have made a speculative effort to associate them with disorders of porphyrin metabolism,[14] at least in part, but we have no confirmative data. This therapeutic use of Frenquel has been a happy revelation, and may well prove to be one of its most practical indications.

By the time the study on post-operative confusion was undertaken we had lost our timidity about the use of higher doses of Frenquel both intravenously and orally. Smaller doses do not suffice in these cases, and it has become our procedure to give these patients 100 mg. Frenquel intravenously *statim* when the post-operative confusional syndrome is diagnosed, and to follow with 100 mg. t.i.d. orally for at least one week. The oral dose is then dropped progressively, and is withdrawn at the end of three weeks, or earlier if the patient is discharged from hospital before that time. Relief of symptoms usually begins within a few hours of the initiation of this regime, and the patient returns to his *status quo ante* mentally in 24-72 hours in just about every case.

Comment

We have been unable to find any toxic reactions or any subjective side-reactions in any of the 115 patients who have been under study in this series. Blood, urine and liver function tests have been carried out on patients who have taken Frenquel for ten or more months, but no pathology has been revealed in the hemopoietic organs, livers or kidneys of the patients studied. As far as we have been able to determine, Frenquel is a wholly safe drug in the dosage range in which it has been used in this study. No incompatibilities with other drugs have been noted, with the possible exception of the sulfonamides. An 81 yr. old man developed post-operative confusion after prostatectomy. This continued for five days despite the use of our usual Frenquel regime. When a sulfa drug he was taking at the same time was withdrawn, he began to clear mentally within 24 hours. We gain the impression from this single experience that sulfonamides may inactivate the drug.

Frenquel is an unusual drug. It produces no symptoms in healthy normal subjects. It seems to have no hypnotic action whatever. Although one is tempted to compare it with chlorpromazine and reserpine, it is our feeling that more thorough investigation will prove that it is quite different from these drugs. Its spectrum of effectiveness is more circumscribed than that of the other two *ataractic*[15] drugs, in that its value as a therapeutic agent seems to be confined to schizophrenia and schizophrenia-like disorders. On the other hand, it does not appear to produce any of the side-reactions such as nasal congestion, jaundice, parkinsonism, apathy, nor the other complications occasionally seen with those drugs. From this it may be inferred tentatively that its mode and site of action is unique.

We are in complete ignorance of the neurochemistry of the compound's action. In his study of the antagonism between LSD-25 and Frenquel in the rabbit brain, Himwich[16] has arrived at the important conclusion that

the reticular activating system of the upper brain stem is the primary site of action of the drug in that animal. Heath and his associates[17] reported that a schizophrenic patient who was improved by Frenquel lost the electrographic abnormality in the septal area which had been present before the drug was given.

The inconsistency of the therapeutic efficacy of this drug in schizophrenia, both of the acute and chronic variety, lends credence to the contention that this disorder is probably a reaction pattern and not a disease entity. Although we are encouraged to believe that another drug has been added to the list of *ataraxics* in addition to chlorpromazine and reserpine, it must be admitted that we know as little about the drug we are using as we do about the diseases we are trying to treat.

Summary and Conclusions

1. The therapeutic properties of Frenquel, alpha-(4-piperidyl) benzhydrol hydrochloride, have been under study for the past twelve months. The foregoing is an account of an exploratory adventure in therapeutics rather than a statistical study.

2. The therapeutic indication for the use of Frenquel appears to be confined to schizophrenic dissociation syndromes, and it is unique in this regard. It is not consistently successful in relieving such disorders.

3. It acts as a partial or complete blocking agent against the development of LSD-25 and mescaline experimental psychoses when it is given as a premedication to healthy subjects who ingest these hallucinogenic drugs. When injected intravenously during the height of such experimental psychoses it brings them to an abrupt end. Preliminary observations suggest that it fails to perform the same function in model psychoses produced by pyrahexyl, a cannabis-like drug.

4. In a small series of cases of acute schizophrenia, Frenquel has relieved the disorder rapidly in about a third of the cases. Electro-convulsive therapy increases the number of favorable responses in this group. After relief of symptoms it appears necessary to keep the patient on a maintenance dose of the drug to prevent relapse.

5. In chronic schizophrenia it is also of therapeutic value in a small number of cases, and its effectiveness appears to be enhanced by the simultaneous use of chlorpromazine and/or E.C.T. on occasion.

6. Preliminary observations suggest that it is also of therapeutic value in some of the psychotic reactions arising out of chronic alcoholism, but inconsistently so, especially in low doses.

7. The periodic dissociation reactions which occur in senile patients with organic brain syndromes have responded to Frenquel treatment in a small number of cases, and we are encouraged to enlarge our clinical observations on this group.

8. In high doses, given both intravenously and orally, the drug has also relieved post-operative confusional states, which in our opinion appear to be quite similar clinically to acute schizophrenic reactions. Larger experience may reveal that this is one of the more hopeful therapeutic indications for the use of the drug.

9. We have given Frenquel for a large assortment of other neurological and psychiatric disorders without benefit. The one possible exception is that of acute intermittent porphyria. In two cases of this disorder abdominal complaints have been minimized, but neurological and psychiatric components of the syndrome have remained unaltered during two months of treatment. A larger and more prolonged series of observations will be necessary to confirm this curious finding.

10. Review of the 115 cases in this study has led to the conclusion that Frenquel appears to be a wholly non-toxic compound, and no subjective complaints of side-reactions have arisen from its use. No incompatibilities with other drugs have been noted, with the possible exception of sulfonamides. In one case of post-operative confusion we gained the impression that Frenquel was inactivated by the simultaneous use of a sulfonamide.

11. As our experience has broadened, we have been emboldened to use Frenquel in higher doses both intravenously and orally. In the acute dissociation syndromes especially, we now give the drug intravenously in 100 mg. doses as soon as the diagnosis is established, and follow with as much as 300-

400 mg. orally per day in divided doses. This appears to enhance the therapeutic benefit of the drug without jeopardizing the health of the patient.

12. Frenquel appears to have a place, though a limited one, along with chlorpromazine and reserpine, among the *ataractic* drugs, i.e., those which bring about *ataraxy,* or freedom from confusion. The drug is worthy of further study.

Authors' Note: Frenquel and Meratran used in this study were supplied by the Department of Medical Research of The Wm. S. Merrell Co., Cincinnati, Ohio.

The authors wish to thank their colleagues, Dr. W. E. Hillard for assisting in the experiments on healthy subjects, and Dr. J. A. L. Moulton for assisting in the patient study.

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Psychodynamics in a Case of Retrocollis

J. MENDELSON, M.D.
Baltimore, Maryland

Introduction

The etiological factors which produce spasmodic torticollis and retrocollis are as yet poorly understood. Opinion is sharply divided as to the relative importance of organic and functional factors which may precipitate the syndrome and the role of such factors in planning therapeutic measures. Hassin[1] has reviewed evidence describing the symptomatology due to lesions of the corpus striatum. Rabiner and Keschner[2] described cases of spasmodic torticollis precipitated by psychological factors but later classified the disease in the dystonia musculorum deformans group. Based upon a purely organic etiology, surgical methods have been advocated for treatment,[3,4] but these have yielded poor results. Studies of changes in muscle potentials of the neck muscles during spasm have been carried out,[5] and while these have been helpful in understanding muscle reaction patterns, they have shed little light on the underlying pathological process in the central nervous system. Recently, Garnett and Elbirlik[6] presented a series of nine cases in which the concept of body image in relation to symptomatology was developed. The role of "organ language" and symbolic postural relationships of the head is stressed by these authors. The special significance of neck and head positions has also been stressed by Walshe.[7] The following case is presented to illustrate some pertinent psychodynamic mechanisms operating in a case of retrocollis.

Case Report

The patient, a 64-year-old colored female, was admitted to the Medical Service of the University Hospital with the chief complaint of shaking of the head. The history of her illness dated back to December 9, 1953 when she first noticed a slight nodding of her head while visiting the Out-patient Cardian Clinic. She states that she did not pay much attention to this symptom initially; however, the nodding gradually became worse so that she was forced to remain in bed most of the time. During this time in bed, she was able to attend to her body needs and was able to eat all her meals by herself.

She was seen in the Neurology Clinic on December 29, 1953 in rather marked distress. Spontaneously, her head would gradually begin to bob in an anterior-posterior direction; this condition increased in severity as the episode continued. The clonic phase of nodding was followed by a tonic hyperextension of her neck until her face was pointed directly upwards. The episode would end rather abruptly with complete relaxation of all the muscles of the body, and the patient would be able to talk coherently until the next episode started a few minutes later. The patient's sensorium was clear at this time. There were no other abnormal neurological findings.

The past history of the patient reveals that she has been a known diabetic since 1951, being placed on a low carbohydrate and fat diet in May, 1951. She has been a known hypertensive the same length of time and was considered to be in mild congestive failure in November, 1953. Other past medical history is not significant.

Physical examination on admission revealed an obese colored female, respiration 20, pulse 80, and blood pressure 210/110. Attacks of head shaking occurred frequently, beginning with violent clonic contractions of the posterior cervical muscles followed by a tonic spasm and hyperextension of the head. During these episodes she was unable to speak but did not seem to be in any pain. The head was always observed to shake in the anterior-posterior direction, and there was no lateral component to the attack.

Positive physical findings were as follows: AV nicking revealed on fundiscopic examination. Cardiovascular examination revealed moderate enlargement of the heart to the left; sinus rhythm with occasional extra-systoles; systolic murmurs were heard in the aortic, pulmonic and mitral areas. Examination of the extremities revealed a chronic lymphedema of the left leg with trophic changes in the skin of both legs. Neurological examination was within normal limits.

Course in the Hospital:

On admission the patient was given a controlled diabetic diet. A lumbar puncture was done the day following admission and revealed no significant abnormalities. The EEG performed on January 4, 1954 revealed diffuse slowing (7-8/sec., 20/50 u v) in the parietal and occipital areas. During episodes of head shaking, high voltage multiple spikking was observed and interpreted as indi-

From the Psychiatric Institute, University of Maryland, School of Medicine, Baltimore.

cative of a diffuse cerebral disorder of a convulsive nature. On January 6, 1954 a neurological consultation was conducted and her illness diagnosed as retrocollis probably resulting from arteriosclerotic changes in the corpus striatum.

The patient's seizures continued during her first two weeks of hospitalization. However, during the third week they stopped suddenly, and as of January 11, 1954 no head shaking of any degree was present. At this time she was also well-controlled on 40 units of NPH insulin. In order to attempt to correlate disappearance of the head symptoms with lowering of her blood sugar level, the NPH insulin was discontinued. A further increase in blood sugar was produced by administering glucose to the patient orally. Although a high level of blood sugar was obtained, no exacerbation of the symptomatology was noticed. From the time of admission she was seen in psychiatric consultations, and these will be discussed below. The patient was discharged on February 3, 1954 to be followed in the cardiac, diabetic and GI clinics. Since the time of discharge, she has had no episodes of head shaking.

Psychiatric Studies:

From the time of admission the patient was seen at least every other day, and interviews were held ranging from 40 to 60 minutes. It was noted during the initial interviews that the patient was extremely sensitive to the attitudes and behavior of all those she contacted in her hospital environment. She seemed to manifest considerable hostility toward the hospital staff, particularly the physicians, and often stated that they were not aiding her as much as possible. The expression of such hostility was not direct and it appeared as if the patient were suppressing her feelings. Any critical remark would be followed by a strongly apologetic gesture such as: "The doctors aren't helping me much, but I know they're trying their best—yes, I know they are—they want to help me." After the first two interviews she began verbalizing about her family and family relations. She spoke of a daughter who had "fits" since she was a small child, describing one component of these "fits" as a hyperextension of the neck. When asked to demonstrate the appearance of her daughter's neck signs, she refused, fearing, she said, that such might "bring on fits" on herself.

The patient verbalized much material concerning the "saving" of her soul and the role of prayer in such. Two salient features appeared in these early interviews regarding exacerbations of head shaking. First, head shaking would be markedly aggravated when any laboratory or diagnostic procedure was performed, and second, head shaking seemed to be aggravated during the times the patient would discuss prayer. These initial interviews seemed to indicate that the patient was having difficulty handling feelings of hostility and that prayer appeared to be closely integrated with the problem.

In order to test the hypothesis that her symptomatology might be related to stress situations involving both hostility and prayer, several structured interviews were designed. Recordings were made of all verbalized material during these interviews. During the first of these interviews, attempts were made to focus upon the patient's feeling about her own soul and prayer. When asked about praying, the patient responded, "I can't help but pray ever since I heard that voice." She went on to describe the voice which she had heard ten years ago in these terms: "I been thinking ever since I heard that voice. Ever since I heard it I been saved. My soul has been saved." (At the word 'soul,' marked shaking of the head was noted.) The patient was asked, "Can you tell me how you felt before you heard that voice?"

Patient: "I was bothered. I was bothered. I couldn't rest."
Doctor: "Could you tell me what that was like?"
Patient: "Well, I was worried, worried."
Doctor: "What was that worry like?"
Patient: "Ain't you never been worried? Ain't you? Ain't you?"

A definite pattern of response was observed to occur at this time. First, when attempts were made to focus upon the patient's worries previous to hearing the voice, she would consistently block. Second, whenever the patient verbalized about her own soul, she would have an exacerbation of head shaking. And third, when the problem of the patient's worrying and her soul were focused upon concurrently, she responded: "Ain't you

never worried about your soul? Well, some folks don't worry about their souls. Lady I worked for many years ago didn't worry about her soul." At this point the patient went on to describe her employer at the time when she first heard the voice. She described this employer in markedly hostile terms. It seemed apparent that the patient tended to relate feelings of hostility in terms of the relative quality of the souls of herself and others in her environment.

During the later interviews, attempts were made to focus upon the patient's prayer and attitude toward prayer in relation to her soul.

Doctor: "Do you pray about your soul now?"

Patient: "Yes, I can't help it, I can't help it, I can't held it."

During this time the patient's head was shaking actively.

Doctor: "Can you tell me what that was like when you said you couldn't help it?"

Patient: "Like those spells I have, like those spells I have. I just couldn't help it."

The patient stated that before she had heard the voice which had told her to "join the church," that she "had been redeemed by the blood of the Lamb," she felt she could not pray for her soul. When asked what that feeling was like, she said: "It was awful. I felt all full up. I felt full up like I would bust." She went on to verbalize how she had often felt angry but couldn't do anything about it. She related that these feelings of anger toward other people were almost unbearable to her before she had heard the voice. Since hearing the voice, however, she stated that "things just don't bother me as much," and said, "I been redeemed, I heard a voice telling me I been redeemed." When the patient was asked, "How do feel now when people do things that make you angry or bother you?" the patient replied, "Well, I worry."

Doctor: "What is it you worry about?"

Patient: "Well, I guess I worry about my soul, and I worry about the souls of the people that make me angry."

Doctor: "And when these people make you angry, do you tell them you're angry?"

Patient: "No, I don't."

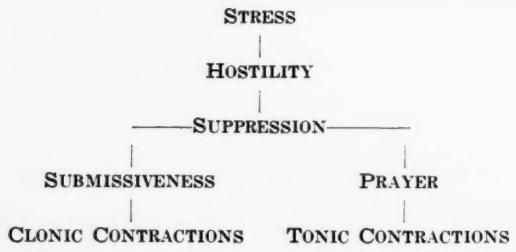
Doctor: "Do you do or say anything?"

Patient: "Well, I guess I just pray."

The patient admitted that when feelings of anger overtook her she did not directly express them toward those who made her angry, but rather she would keep these feelings inside. The only form of relief from the "full-up" emotions that she felt was prayer. It is noteworthy that the patient related that in the actual act of praying she would assume a characteristic physical position of looking upwards, as she stated, "I look to God—I look to Heaven."

Discussion

Garnett and Elbirlik[6] stated in their series of cases, "It seems to us that in all of our cases the symptom of torticollis was an eloquent expression of the patient's conflict or dilemma." The state: "The general impression we got was that these patients are actually people of considerable superiority, perhaps more intelligent, more sensitive, more aware, more perceptive than the average, or at least those with whom the patient had to cope or put up with; that the symptoms did perhaps mean a looking away from something intolerable or painful in the immediate environment. In some cases it may also mean the shame felt by those close to him or perhaps the shame felt at his own surrender to some attitude or situation he feels to be inconsistent with his own true nature. In the symptom of turning the head to one side while the body remains straight may be acted out the patient's saying, 'My body goes along like everyone else's, conforms to what is expected, but I, as represented by the head, could not do so. I walk one way and look in another direction.'" The other direction in which the patient looked was obviously toward heaven. In prayer, the patient found a method of handling suppressed hostility produced by injustices she felt were thrust upon her. It was as if she were saying all things would be different in Heaven. If one reconsiders the pattern of head shaking, the initial clonic phase (nodding) could correspond to initial submissiveness or nodding affirmation whereas the second and tonic phase of hyperextension could correspond to her looking toward Heaven as a defense for the anxiety aroused by her hostility. The following diagrammatic scheme may help to exemplify this:



The problem arises as to the relative role of specific factors operating in this patient. It is most difficult to assess the interplay of such factors. The presence of long-standing diabetic and arteriosclerotic vascular changes certainly must be considered as a possible etiologic factor in initiating cerebrovascular pathology. In addition, the electroencephalographic findings strongly support the presence of diffuse abnormality of the electrical activity of the brain. However, these findings alone cannot account for the patient's symptoms. The abrupt cessation of the retrocollis corresponded with the increasing ability of the patient to directly verbalize hostile feelings without utilization of prayer as a defense mechanism. When this had occurred subsequent attempts to increase organic dysfunction, i.e., discontinuance of insulin and administration of glucose orally, did not produce an exacerbation of symptoms. It is of interest that the patient responded to such attempts by direct verbalization of her hostility with no apparent suppression. Thus active symptoms depended on the presence of both organic pathological processes and specific psychological patterns. The concept presented by Walshe[7] seems appropriate when considering such a point of view. He states: "Recently it has been suggested that a local lesion in the corpus striatum may provoke torticollis as a form of 'release symptom,' and it is true that severe examples of this spasm have been found to follow epidemic encephalitis. Even so, the hypothesis is without any satisfactory basis. Psysiologically, torticollis may be regarded as a disorder in the carriage of the head, a complex function peculiar to man, for the head of the quadruped is suspended. It is such recently evolved functions that are so vulnerable to disturbance from factors other than gross focal lesions. It is in short impossible to asses the relative role in its causation of physical and psychological factors. . . . Spasmodic torticollis is a comparatively rare affection, a fact which in view of the widespread incidence of psychoneurosis may be taken to indicate that this appearance depends upon the rare coincidence in a given subject of the necessary physical and psychological factors." It is believed that the patient presented, exemplified the combination of the physical and psychological factors which precipitate and maintain this unusual syndrome.

Author's Note: The author wishes to express his thanks to Dr. Jacob E. Finesinger and Dr. Enoch Callaway for their advice in reviewing this case and for their assistance in the preparation of this manuscript.

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On Pseudo-Naiveté Displayed When Confronted With Personal Attacks

EDMUND BERGLER, M.D.
New York, New York

> The belief in a supernatural source of evil is not necessary; men alone are quite capable of every wickedness.
>
> *Joseph Conrad.*

In general, people are aware that malice surrounds them, and that they themselves are no less generously endowed with this trait than their fellow beings. This general knewledge is reflected in such common expressions as "Human nature being what it is," and "You know how people are" and "Now, is'nt that a typically catty remark?" and dozens of others.

Somehow, this knowledge is shoved far into the background—or it may even totally evaporate—when a malicious personal attack on oneself is to be dealt with. On these occasions, a person who is ordinarily a connoisseur of human malice becomes an incredulous child: "I can't understand why he's going out of his way to hurt me like that!" a bitter and astonished contemporary will complain.

The irony of the situation lies in the complainer's presumption that he, and he alone, was immune and would not be attacked. If people are "malicious on principle," why should even one's wonderful self be excluded as the butt of an attack?

In analyzing this pseudo-naivete, one finds that a specific unconscious mechanism is at work. If one's general knowledge were applied to the specific situation when the problem is a personal attack, much of the indignation and many of the complaints would automatically become superfluous, although the reaction would still be anger plus a search for a means of defending oneself and eventually retaliating. The typical defensive program would be no different if the feeling of deep indignation were omitted.

One gathers the impression, therefore, that "deep indignation," helped along by spurious naivete, is a valuable and almost indispensable part of the psychic menu in these situations.

This impression is borne out by the clinical facts. A more rational approach could be achieved if human malice were accepted as unavoidable, but something in the psychic apparatus prevents this desirable state of affairs.

In periods of emotional serenity, people invariably make use of their knowledge of the universality of malice; if they were equally conscious of this elementary rule in the emotionally charged situation of being personally attacked, they would be barring the way to a *masochistic elaboration* of the conflict. It seems that this opportunity for masochistic misuse is too good to pass up. This accounts for the appearance of pseudo-naivete.

Admittedly, this statement is paradoxical. Why should each and every person be so eager to misuse, masochistically, attacks made upon himself?

Before explaining that paradox, it is fitting to state that the attacked person reacts paradoxically: although he is quite familiar with human malice in *general,* he forgets his knowledge when the malice is directed *specifically* against himself. Hence a reminder is necessary: the "paradoxical" interpretation is *preceded* by an equally paradoxical behavior pattern in the person observed.

*

Personal attacks are of two kinds: those that are *unconsciously self-provoked,* and those that are perpetrated on an *"innocent bystander."* In either case, the reaction of the person attacked is deep indignation.

The *unconsciously self-provoked attack* follows the general rules for the clinical picture of the masochistic "pleasure-in-displeasure" pattern, as summarized in my book, *The Superego* (Grune & Stratton, New York, 1952):

a. Through their behavior, or the misuse of an external situation, neurotics unconsciously provoke disappointment and refusal, identifying the outer world with the "refussing" pre-Oedipal mother.

b. Not realizing that they themselves have

brought about this disappointment, they become pseudo-aggressive, acting in righteous indignation and seemingly in self-defense.

c. They then consciously indulge in self-pity, unconsciously enjoying psychic masochism: "This can happen only to me."

The deep indignation felt by these neurotics is thus part and parcel of the disguise (for the benefit of themselves and of their superegos) which purports to show them as victims of kicks, not lovers of kicks. *In inner reality, they get a "kick" out of being kicked.*

*

The situation of the "innocent bystander" under attack is more complex. A series of parallel processes is set in motion:

First, the *conscious* attempt to point out the error; this can be compared with the innocent man's assertion, "You got the wrong man, sheriff!"

Second, the superego's *unconscious* attack, in which the ego is accused of two crimes: "Are you really innocent?" and "You are enjoying this miserable situation!" The inner torturer—and the unconscious conscience is exactly that—"makes a case" out of innuendoes of guilt pertaining to *other* situations, in which the victim was not innocent, and at the same time alludes to remnants of psychic masochism present in everyone.

Third, the unconscious ego's *counteraction,* which is a denial of both accusations leveled by the superego. The accent may be on the defense against the charge of masochism, or on the assertion of innocence in the specific situation, depending on the ready-to-use inner quantities. The unconscious ego then turns the tables in a maneuver which resembles a preventive "public relations operation." Instead of simply refuting the charge, the charge is powerfully and indignantly denied. In this way, *an argument is put in storage* for use when the next attack—as is inevitable—is forthcoming from the superego. On this next occasion the charge may be justified, and therefore the ego holds in readiness the defense prepared when the reproach was unjustified: "I'm as innocent as I was that last time!"

*

The grotesque result is that in both instances—the unconsciously self-provoked attack and the "innocent bystander" situation —"deep indignation" comes to the fore, and this indignation is made possible by pseudo-naivete. However, the reasons for the use of pseudo-naivete as a tool and of indignation as a defense are different in each case.

In the self-provoked attack, pseudo-naivete is an integral part of the game of self-deception played for the benefit of one's self and one's superego, the game of acting the innocent victim. In the innocent bystander situation, pseudo-naivete is used to prove that the victim adheres to the precepts of sweetness and light, and that his only nourishment is the milk of human kindness. "How can people be so mean and malicious?" he asks, gratuitously forgetting what he has learned from life. Moreover, by pronouncing absence of malice as the predominant human trait, he achieves an implied negation of the masochistic misuse accusation. If malice is but an exception, how can he misuse it *typically,* as the indictment of the inner conscience claims?

Human malice (especially when exaggerated) is a neurotic defense. In a person constantly accused by his inner conscience of psychic masochism, the defense reads: "How can I be masochistic? Look how aggressive I am!"

As soon as the easy-going attitude of "live and let live" is abandoned (or no longer discernible) in a personality, neurotic vicissitudes are to be expected. Neurotic malice, covering neurotic psychic masochism, is predominant among these. Both the end result of the infantile conflict and the defense against it use pseudo-naivete as covering cloak.

The Changing Attitude Towards Mental Retardation

HANS MEYER, M.D.
Butlerville, Indiana

Research workers interested in the causes of mental retardation drew attention to the incidence of infections during pregnancy as one possible cause. In the hope of being able to make a contribution, I sent out a questionnaire to the parents of all patients in Muscatatuck State School in Indiana. The result of this questionnaire is meager and summarized in Table I. Two-thirds of the parents, however, felt the need to give additional information. A wealth of interesting material was obtained this way. From the many details of psychiatric interest, a certain pattern of changing attitude towards the occurrence of a mentally retarded patient in a family can be found:

I. Guilt feelings occur invariably in parents facing the arrival of a mentally retarded patient. They look for a scape-goat to project these feelings into and make them acceptable to themselves. It is easy to understand that one of the main scape-goats is the physician. Questionnaires returned for older patients will contain sentences like this: "If we would have had a competent physician, nothing would have happened." "The doctor injured the vocal cords at birth, and now the child cannot speak." "The doctor missed his bet and the child was born too early." In patients that are now in our Nursery, however, sentences like this are to be found: "We have no quarrel with the obstetrician." (!) Older questionnaires accuse giving of too strong a medicine, especially Calomel, newer ones say: "The blood transfusion came too late."

II. Superstitions are still found in questionnaires of older patients like the following: "My husband scared me with an ox-head." "A fox scared me during pregnancy." For younger children one reads of "mistreatment during pregnancy," with or without body blows, and of the now very fashionable "fall on the head." Car accidents during pregnancy, or occurring to the patient before admission, appear more and more as spontaneously given "causes" of the present condition.

III. Direct hostility against the present questionnaire and the institution have changed in pattern likewise. In questionnaires filled out by older people, one reads: "I don't know why my child had to be brought there." For younger children disappointment is expressed that not more progress was achieved.

IV. The attitude towards syphilis as cause of the patients condition has changed likewise. Older questionnaires read: "I always lead a clean life." "There has been no syphilis in our family." This answer comes often misinterpreting the questionnaire. In somewhat younger patients the occurrence of syphilis in the family is openly accused of having been the cause of the mental retardation. The husband or wife accuses the mate, sometimes in a paranoid fashion. In the youngest generation, however, syphilis is never mentioned.

V. Tuberculosis is mentioned twice. In one patient, the history is that the mother died of the disease and apparently had had it during the entire pregnancy. The patient is an interesting overlay of mental retardation and psychosis but has no tuberculosis. The other patient is on our Tuberculosis Ward. Not returned were questionnaires of other patients on the Tuberculosis Ward and of those where tuberculosis would have been the cause indeed. Two nursery patients had been doing well until they got tuberculous meningitis. Treated with antibiotics, these children, formerly doomed to die, were saved. But an empty shell remained which belongs to our institution.

VI. The most interesting and challenging contributions come from families where incidents of mental illness have occurred and are put on one and the same level with the mental retardation of the present patient. In the questionnaires of older patients one will

From Muscatatuck State School, Butlerville, Indiana, Alfred Sasser, Jr., Superintendent.

read that "this condition ran in the family," whereas in questionnaires returned for younger patients one will read: "I need psychiatric help myself, can you get it for me?"

VII. The pattern of changing attitude shows up clearly even in those answers where no apparent reason can be found. These answers are, of course, quite numerous. The typical expression in a questionnaire for older people is: "I do not know how such a condition could occur in our family." The typical answer for one of the younger patients is: "I was told Mongolism would not occur twice in the same family but it did." One mother, very active in the parents' movement, writes that she had, by her first marriage, two healthy children; by her present marriage, there were four children born, one died at birth, they all were Mongoloids: "But we are not ashamed of it at all."(!)

VIII. This changing attitude toward the occurrence of mental retardation goes parallel with an increasing acceptance and re-acceptance of the formerly rejected institutionalized child. Quite a few guilt-ridden parents who had been full of complaints when the child was admitted, develop into interested helpers. The institutions change from custodial care to active treatment centers. More and more patients get ready to leave the institution. The changing attitude of the family is preparing the community for its responsibility of re-accepting former patients.

Summary

1. Questionnaires were sent out to inquire into the incidence of infections during pregnancy as possible cause of mental retardation. The results are given.

2. The attitude of relatives towards institutionalized patients with mental retardation seems to have changed. Examples from the questionnaire are given and seem to follow a pattern.

3. Parallel with the change from custodial institutions to treatment centers, an increasing acceptance and re-acceptance of institutionalized mentally retarded children in family and community seems to take place.

TABLE I

Musctatuck State School, Butlerville, Indiana

Questionnaires on Infections During Pregnancy

No. of Questionnaires sent out	2000
No. of Questionnaires answered	582
%	29.1
No. of Questionnaires answered	582
No. of Questionnaires answered, "yes"	47
%	8.08
No. of Questionnaires answered, "yes"	47
No. of Questionnaires added	3
Together	50

TABLE II

Accused Infection During Pregnancy

(In the wording of the answers:)

GROUP I

"Flu"	13
Three-Day Measles	3
Measles	1
Mumps	1
Diphtheria	1
Undulant Fever	1
Tonsillitis	1
Sinusitis	1
Gum Infection	1
Lung Abscess	1
Pink Eye	1
Appendicitis	1
Felon on Thumb	1
Together	27

GROUP II

Kidney Infections, Urine Poisoning	14
Syphilis	4
Tuberculosis	2
"Heart and Nerve Trouble"	2
Hay Fever	1
Together	23

Use of Reserpine (Serpasil) in Psychotic Patients

(A Preliminary Report)

JAMES WEISHAUS, M.D.
Los Angeles, Calif.

Extracts of the roots of *Rauwolfia,* a small shrub growing wild in India and other tropical and subtropical regions, have been used in Ayurvedic medicine for centuries.[1] Known as the "insanity herb" in the bazaars of certain Indian provinces,[2] rauwolfia has been termed a "cure" since ancient times for many widespread conditions, including mental illnesses.[3]

Recently, Hakim,[4] an Indian psychiatrist, reported a recovery rate of 51 per cent in 146 psychotics treated with a preparation composed half of rauwolfia and half of five other herbs or plants. He also reported a recovery rate of 80 per cent when the drug was combined with electroshock treatments, as contrasted to a recovery rate of 31 per cent for EST alone.

With the isolation, purification and introduction of reserpine,[5] a crystalline alkaloid of rauwolfia root, new impetus was given to the study of rauwolfia in various conditions. Reserpine was demonstrated to be the chief active principle of rauwolfia,[6] with a therapeutic ratio of approximately 1000 to 1 compared with the whole root.

Since the drug is believed to act chiefly in the region of the hypothalamus,[7,8] in which are located the chief central mechanisms through which emotional behavior is mediated, it offered a new approach to the treatment of the mentally ill. It is neither a ganglionic blocking agent nor an adrenolytic agent and does not appear to have any direct action on the cerebral cortex.[9]

Kline,[10] who administered reserpine to 411 mental patients, of whom 94.4 per cent were diagnosed as schizophrenic, reported that it made patients more relaxed, more sociable, more communicative and more amenable to psychotherapy.

Noce, Williams and Rapaport[11] declared that raucous, hyperactive, combative and uncooperative patients became friendly, cheerful, sociable and cooperative after the administration of reserpine, and that seclusion, restraints, sedation with barbiturates and electroshock therapy were eliminated in most cases.

From Brentwood Neuropsychiatric Hospital, Veterans Administration Center, Los Angeles, Calif.

Scope of Report

This report covers the use of Serpasil (reserpine CIBA) in various types of mentally disturbed patients over a period of six months, starting in April 1954. An attempt has been made to evaluate the effect of the drug in terms of symptomatic changes. Since the study was in the nature of a preliminary survey, no controls were set up other than the condition of the patients before, during and immediately following the use of the drug.

Twenty-five male patients on various wards of the hospital were started on Serpasil, but 15 discontinued the use of the drug for various reasons, such as leaving the hospital (4 patients); refusal of the patient to cooperate in taking the drug (4 patients); administration of ECT or other forms of therapy (3 patients); nausea, vomiting, etc. (2 patients); discharged as improved (1 patient); apparent aggravation of symptoms (1 patient). Most of the 15 had shown some improvement with Serpasil, but were observed for too short a period to arrive at definite conclusions. Of the ten patients who continued to take the drug, eight have been followed for over four months.

In general, side effects of Serpasil have been minor and easily controlled by adjusting the dosage or temporarily discontinuing the drug. Reactions noted most frequently were initial giddiness and mild drowsiness. Some patients reported vivid dreams and increased frequency of bowel movements.

Case Histories

Following are brief case histories reviewing the clinical courses of the eight patients.

A 24-year old white male hospitalized on two occasions since October 12, 1951, for a psychotic reaction manifested by hallucinations and continuous preoccupation with religious thoughts. Most recent admission August 20, 1953. History of previous treatment includes 23 insulin coma treatments, 119 electroshock treatments prior to admission to this hospital because of delusions, hostility and generally disturbed behavior. He was given 20 electroshock treatments in one course, with some improvement, but then relapsed and again was placed on insulin coma treatments and electronarcosis, receiving a total of 93 treatments with very little improvement.

In April 1954, prior to being placed on Serpasil, he was described as restless, assaultive without provocation, and unable to tolerate much frustration. His assaultiveness was so intense that for a period of 28 treatments he was given 2 electroshock treatments per day. On June 2, 1954, the patient was placed on 2.0 mg. of Serpasil orally and 5.0 mg. intramuscularly every day. His behavior continued to be disturbed, requiring occasional shock treatments, together with physical and chemical restraint for the next several weeks. During this time the Serpasil dosage was increased to 12.0 mg. per day and then to 17.0 mg. a day.

Beginning July 8, the patient showed a markedly improved adjustment to other patients and to ward routine and restrictions. Electroshock therapy was gradually discontinued and the last necessary treatment was July 19. There continued to occur occasional episodes of hyperactivity which were controlled by room seclusion, but it has not been necessary to restrain the patient either physically or chemically for several months. In fact, his adjustment has so improved that he has received a privilege card and has gone out on several successful passes.

Case No. 2—W.B.

A 24-year old white male hospitalized since October 1951, because of hallucinations and delusions, with a diagnosis of schizophrenic reaction, paranoid type. He received 23 electroshock treatments and 24 insulin coma treatments with some improvement, but continued to have delusions and hallucinations. At times he was acutely disturbed, tense, agitated and panicky. His adjustment to the hospital routine was difficult.

In June 1954, after being in group therapy for 3 months, and because of a continuation of symptoms, he was placed on Serpasil, beginning with 2.0 mg. orally per day and increasing to 4.0 mg. per day. Since then he has shown improvement. He has required other heavy sedation much less frequently. His restlessness and disturbance in response to hallucinations are markedly diminished.

At times the patient becomes somewhat upset, but these episodes are more easily controlled. For the first time since his hospital stay, he has been able to accomplish good work in an industrial assignment for several months. His therapist also reports that he seems more able to participate in group therapy because of the diminution in his general tension.

Case No. 3—E.C.

This 28-year old white male first became ill about 1947. He was most recently hospitalized in May 1952. He has received some insulin coma treatments and intensive psychotherapy. His diagnosis is schizophrenic reaction, paranoid type. His symptoms include ideas of reference and persecution, hallucinations, several suicidal attempts, irritability, impulsive assaultiveness and some alcoholism.

For the past year the patient has appeared to be confused, withdrawn, seclusive and delusional. He has been in psychotherapy and there has seemed to be some gradual improvement. However, he complained of feeling overwhelmed with anxiety, hostility, guilt and fear over punishment and it was thought that he might benefit by sedation with Serpasil. On two occasions, for instance, he was so tense in the therapeutic sessions that he vomited upon coming into the office.

After the patient was placed on 2.0 mg. of Serpasil per day orally, he apparently relaxed to the extent that he became more sloppy in his appearance, less concerned, and began to be a problem because of his continual fatigue and lack of motivation. He would leave his pants unbuttoned, place his shoes on the wrong feet and generally give the appearance of marked apathy concerning his surroundings and personal appearance. Because of this apparent regression, the patient was taken off Serpasil several months later. No great change otherwise was noted in the patient.

Case No. 4—J.M.

A 32-year old white male admitted for the third time in April 1954. His illness first began in 1945 with ideas of reference, confusion and disorientation. Diagnosis: Schizophrenic reaction, paranoid type. Since 1945, the patient has been in many difficulties. He was arrested for house breaking, fought with his father and abused his wife. For some years there has been a gradual deterioration in his behavior. He was unable to hold a job, was morose, irritable, occasionally belligerent and assaultive. He had received electroshock therapy with no improvement.

Upon admission the patient was noted to be depressed, restless, belligerent and irritable, with feelings of persecution. At times he would show impulsive, hyperactive behavior. On one occasion he attempted to strangle his father, who was visiting with him.

In May 1954, the patient was placed on Serpasil, 2.0 mg. per day, with an almost immediately noticeable effect. He appeared quieter, more pleasant, gradually became more sociable, and seemed to be no longer hostile and withdrawn. In June he was noted to be enjoying playing baseball with other patients.

On one occasion, because there seemed to be a

temporary recurrence of his hostile, disturbed behavior, Serpasil was increased to 3.0 mg. per day and 5.0 mg. was given intramuscularly. Following this, the patient again became pleasant and cooperative, and was able to go out on passes with his relatives. Because of a markedly improved adjustment to his family and to the ward routine, he was shortly thereafter discharged to a trial visit with his family. At the time of his discharge, the Serpasil was discontinued. No follow-up report is as yet available.

Case No. 5—J.C.

A 36-year old white male admitted many times to this hospital, the last time being in June 1953, by commitment. Patient has had many diagnoses, ranging from constitutional psychopath to manic depressive, manic. Throughout his many hospitalizations, recurrent alcoholism played an important part. His symptoms have consisted of agitation, restlessness, hyperactivity, depression, anxiety, bizarre behavior and impaired judgment. In the past year his adjustment to the hospital routine was chaotic. He went AWOL and became intoxicated, manifesting other erratic behavior.

In March 1954, the patient was placed on an Antabuse program to attempt to control his excessive drinking, but without result. Following an acutely disturbed episode in April 1954, he received a course of electroshock therapy. After 9 treatments, his psychosis remitted but his behavior continued to be hyperactive. There was a marked emotional instability, histrionic gestures and a restless type of hyperactivity.

In June 1954, the patient was placed on Serpasil, 2.0 mg. orally every day. Within two weeks, he had settled down both in his manner and speech and shortly thereafter was given privileges and passes. Subjectively, he felt much more relaxed and in control of his feelings; objectively, he slept well, required no other sedation, was cooperative and quiet and emotionally stable. Subsequently he was discharged to a trial visit, continuing the same dosage of Serpasil. He has been adjusting adequately for two months on trial visit.

Case No. 6—M.T.

A 43-year old white male admitted for the first time in October, 1953. Discharged from the Marine Corps in 1945, with a diagnosis of manic depressive psychosis. Patient had had extensive psychological treatments, including some hospitalization and carbon dioxide treatment in the years 1946 through 1950. His presenting complaints were agitated behavior, abusiveness, violent and hyperactive behavior, impaired judgment, restlessness, alcoholic excess.

In this hospital the patient displayed a markedly variable mood. At times he was quite pleasant, at other times he was extremely sarcastic, bitter, paranoid, nagging and critical. He received a course of shock treatments with considerable improvement and a lessening of his emotional instability.

Following this, the patient was discharged to a trial visit with his wife and at about that time, May 30, 1954, he was started on Serpasil, 2.0 mg. orally every day, in an effort to help him control emotional instability. In June, 1954, the dosage was reduced to 0.5 mg. every day because of patient's marked complaints of headaches, drowsiness and some difficulty in focusing his eyes. These complaints then disappeared and thereafter the dosage was increased to 1 mg. a day orally.

Several weeks later, because of an increase in emotional instability, the dosage was again increased to 2.0 mg. per day. Patient has been able to work at his previous job while on his trial visit. Despite a number of upsetting episodes which he would have been unable to handle previously, he has continued his vocational adjustment. The Serpasil dosage has been adjusted to 1.5 mg. orally every day and on this level the patient is adjusting adequately. For several months he has held two jobs. Both he and his wife report that his emotional instability seems to be relieved by the continued use of Serpasil.

Case No. 7—F.W.

A 62-year old white male diagnosed chronic brain syndrome, associated with convulsive disorder and psychotic reaction. He was most recently hospitalized in March 1953, after creating a disturbance. He had a number of previous hospitalizations, had always been somewhat of a management problem, but more so recently because of his demanding attitude, argumentativeness, paranoid ideation, inability to tolerate frustration and explosive temper. Patient has frequent grand mal and petit mal seizures and has been taking diphenylhydantoin and phenobarbital for many months.

Prior to May 1954, when the patient was first treated with Serpasil, he has displayed frequent emotional upsets, characterized by extreme belligerence, intolerance to other patients, negativism, altercations, antagonistic and abusive manner. Following the administration of Serpasil, 2.0 mg. every day orally, he continued to have occasional seizures, both petit mal and grad mal, but his disturbed behavior diminished considerably. Occasionally he talks loudly and becomes somewhat threatening, but in general he is much more tractable and more pleasant to the personnel and the patients. He is able to control his emotional outbursts more easily and is not so readily disturbed by necessary restrictions and control. The patient has become an easier management problem and seems more satisfied with the hospital routine.

Case No. 8—M.C.

A 55-year old white male who entered this hospital September 27, 1951, because of an acutely agitated, delusional, psychotic state. Following his admission, he had recurring episodes of agitated, delusional, negativistic, uncooperative behavior, requiring short periods of closed ward care with hydrotherapy and chemical sedation. At times he im-

proved, but was generally mildly confused and disoriented. He also had a chronic bronchial asthma, associated with bronchiectasis and emphysema.

For one year prior to being on Serpasil, his mental status and adjustment to the hospital had remained essentially unchanged. He was often a ward management problem because of his loud, threatening, boisterous manner and agitated behavior, complaints and delusions, demands to be put to death and other bizarre ideas. Electroshock therapy resulted in improved mood and emotional stability only while he was receiving it.

In June 1954, the patient's maintenance electroshock therapy was gradually discontinued and at the same time he was placed on Serpasil, 2.0 mg. per day. Thisc was increased to 3.0 mg. on July 29. On September 2, because of the continuation of outbursts of noisy, profane language, negativism and disturbed behavior, he was administered 5.0 mg. of Serpasil intramuscularly plus the 2.0 mg. orally. His behavior immediately improved but on September 5 he began to complain of not feeling well.

On September 13, the patient showed definite evidence of malaise with dyspnea and pallor, but no positive physical findings were noted on a complete physical examination. It was recommended that Serpasil be discontinued. The following day the patient was over his malaise and dyspnea and was reported to be feeling fine. His physical condition has remained good since then, but he has not been placed on Serpasil again.

Summary

From this limited study, it appears that Serpasil in dosages ranging from 2.0 mg. to as high as 17.0 mg. per day is of benefit in the hospital management of various types of behavior disturbances.

In a number of schizophrenics Serpasil was helpful in relieving assaultiveness, tension, restlessness, noisiness, agitation and low frustration tolerance. Because of the resulting relaxation, disturbed patients became more amenable to psychotherapy and other rehabilitative procedures.

In one case of emotional instability characterized by restlessness, impulsive behavior and mood swings, the drug enabled the patient to remain relatively adjusted outside the hospital. In another case of paranoid personality associated with brain damage, the drug favorably influenced the patient's hospital adjustment.

With one withdrawn schizophrenic patient, however, the relaxing effect of the drug seemed to lead to deterioration, with the result that he became more of a management problem than before.

Serpasil proved to be an effective sedative in a number of cases where other types of sedation or treatment aimed at controlling disturbed behavior had been relatively ineffective. Side effects have generally been minor and easily controlled by adjustment of dosage.

It is urged that further studies concerning the use and mode of action of Serpasil in the treatment of neuropsychiatric disturbances be instituted.

Author's Note: Serpasil used in this study was generously supplied through the courtesy of CIBA Pharmaceutical Products, Inc., Summit, New Jersey.

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